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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,507	11/28/2001	Laixin Wang	3302.2.1	3067

21552 7590 09/21/2004

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/996,507	Applicant(s) WANG, LAIXIN	
	Examiner Richard Schnizer, Ph. D	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-83 is/are pending in the application.
- 4a) Of the above claim(s) 65-83 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

An amendment was received and entered on 6/21/04.

Claims 65-83 were added as requested.

Newly submitted claims 65-83 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: these claims are directed to methods of making a carrier for transporting a polycationic macromolecule across a membrane of a cell by covalently linking two or more polycationic polymers to a biocompatible hydrophilic backbone polymer. Previously under consideration were claims 1-47 drawn to compositions, claims 48-64 drawn to methods of using the compositions. New claims 65-83 are related to claims 48-64 as process of making and process of using the product of claims 1-47. Since the product is not allowable, restriction is proper between said method of making and method of using. The product claim is currently being examined along with claims to the process of using it (MPEP § 806.05(i)). Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 65-83 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-64 are under consideration in this Office Action.

The polycationic polymer species "polylysine" is disclosed by Schacht et al (see rejections under 35 USC 102 below), and was rejoined in the Action sent 2/17/04.

Claim Objections

Applicant's amendments were sufficient to overcome the previous objections to claims 17, 30, 48, and 56. Claim 17 is objected to for lack of subject-verb agreement. The second instance of "is" should be "are".

Claims 30 and 56 are objected to because the recited tetrapeptides are not identified by SEQ ID NO. Insertion of "(SEQ ID NO:2)" after the first tetrapeptide, and insertion of "(SEQ ID NO:1)" after the second tetrapeptide is suggested.

Claim 48 is objected to because the second instance of "polymer" should be plural.

Drawings

Applicant has submitted drawings which are accepted for the purpose of examination.

Rejections Withdrawn

The rejection of claims 1-64 under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's amendments substituting "membrane" for "biological barrier".

The rejection of claims 8, 12-16, 20, 21, 38-40, 57-59, and 61 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9-15, 17, 20, 22-25, 27, 30-39, 41-44, 48-51, 53-58, 60, and 61 stand rejected under 35 U.S.C. 102(b) as being anticipated by Schacht et al (WO 98/19710, published 5/14/98).

Schacht teaches synthetic polymer-based carrier vehicles for nucleic acid delivery to cells, and methods of use. Complexes of nucleic acid and polycations such as PEI are formed, and then hydrophilic polymers are used to cross link the polycations. See e.g. abstract, page 3, lines 1-31, and Fig. 1. The hydrophilic polymer may be PEG or HPMA. See page 6, lines 18-24; page 9, lines 28-35, and page 25, lines 25 and 26. The polycation may be polyethyleneimine, polylysine or polyallylamine, etc. See page 25, lines 28 and 29. The compositions may comprise cell polypeptide targeting moieties and membrane disrupting agents such as fusogenic peptides. These agents and moieties may be linked to either the polycation or the hydrophilic polymer. See page 4, lines 10-26; page 6, lines 3-17; page 19, lines 14-19; and paragraph bridging pages 46 and 47. The hydrophilic polymers and polycations may be linked by peptide linkers comprising the sequence GlyPheLeuGly. See paragraph bridging pages 10 and 11. the molecular weight of the hydrophilic polymer may be about 20,000 Da. See page 14, lines 28-30. The molecular weight of the polycation may be 3-2 kDa. See page 10,

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lines 9-17. The nucleic acid may be plasmid DNA, RNA, ribozyme, or antisense oligonucleotide. See e.g. page 10, lines 1-3, and claim 42 at page 57.

Thus Schacht anticipates the claims.

It is noted that US Patent 6,312,727 is a continuation of WO/98/19710, and discloses all of the information set forth therein.

Response to Arguments

Applicant's arguments filed 6/21/04 have been fully considered but they are not persuasive.

Applicant states that the term "backbone" refers to "the single anchoring biocompatible hydrophilic molecule to which the multiple polycationic polymer molecules are linked." Applicant contrasts this with the invention of Schacht and alleges that Schacht does not teach a carrier in which the backbone molecule is a biocompatible hydrophilic polymer. Applicant argues that in Schacht, the polycationic polymer serves as the backbone to which multiple hydrophilic polymers are attached. Applicant concludes that in view of the clear structural differences between the carriers and complexes in Schacht and those of the instant invention, the rejections should be withdrawn.

Applicant's arguments are unpersuasive because they are based on an arbitrary designation of what constitutes a "backbone". Applicant has presented no evidence or reason why the hydrophilic polymer of Schacht cannot be considered a backbone which cross links polycationic polymers. More importantly, Applicant has failed to point out

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any specific limitation of the claims that is not taught by Schacht. If Applicant believes that there are definite structural differences between the compositions, then the claims should be amended to require one or more of these differences. The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 17, 18, 19, 28, 29, 31, 46, 47, 48, 63, and 64 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer.

Schacht teaches that the hydrophilic polymer is multivalent and has more than one reactive group for crosslinking to the polycationic polymer. While Schacht does not explicitly teach that more than two polycationic polymers are crosslinked by a given hydrophilic polymer, Schacht does teach at column 6, lines 27-60 that crosslinking of polycationic polymers with a hydrophilic polymer can stabilize the polycation/nucleic

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acid complex. It would have been obvious to one of ordinary skill in the art at the time of the invention to cross link polycations with hydrophilic polymers as taught by Schacht. The number of crosslinks between the polycations and the hydrophilic polymers is considered to be a matter of design choice that affects the stability of the complex, and would be routinely optimized by one of ordinary skill in the art. Absent evidence of unexpected results, formation of complexes having 8-15 polycations crosslinked by a hydrophilic polymer is considered to be obvious.

Thus the invention as a whole was prima facie obvious.

Claims 1, 7, 8, 17, 25, 26, 31, 45, 48, and 52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98) in view of Bayley et al (US Patent 5,777,078, issued 7/7/98).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer. The complexes may comprise lytic peptides that degrade membranes, thereby allowing delivery of the nucleic acids. See page 4, lines 20-24; page 19, lines 14-19; and page 47, lines 6-12.

Schacht does not teach the use of streptolysin O as a lysis agent.

Bayley teaches compositions for improving DNA uptake into cells, comprising a lytic agent attached to a targeting ligand. The lytic agent may be streptolysin O. See column 1, lines 47-59 and column 2, lines 13-21.

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It would have been obvious to one of ordinary skill in the art at the time of the invention to use as a lytic agent in the invention of Schacht streptolysin O. One would have been motivated to do so because Bayley teaches that streptolysin O is useful for forming pores in membranes to allow delivery of nucleic acids.

Thus the invention as a whole was prima facie obvious.

Claims 1, 16, 17, 21, 31, 38-40, 48, 57, 59, 60, and 62 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98) in view of Wagner et al (US 2001/0005717, published 6/28/01).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer. Schacht does not teach polycations in the range of 400-2000 Da.

Wagner teaches complexes of PEI and nucleic acids wherein the PEI is modified with a hydrophilic polymer. The PEI may have a molecular weight in the range of 700-2,000,000 Da. See paragraph 20 on page 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PEI of molecular weight 700 in the invention of Schacht. One would have been motivated to do so because Wagner teaches that smaller PEI molecules are less toxic. See paragraph 20 on page 2.

Thus the invention as a whole was prima facie obvious.

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Claims 31, 32, and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (WO 98/19710, published 5/14/98) in view of Boggs et al (US Patent 5,681,747, issued 10/28/97).

The teachings of Schacht are reviewed above. Briefly Schacht teaches complexes and methods for delivering polyanionic molecules to cells. The complexes comprise polycations bound to the nucleic acid, and crosslinked with a hydrophilic polymer. Schacht does not teach chimeric RNA/DNA oligos, phosphorothioate oligos, 2'-O-methyl oligos, PNAs or morpholino conjugates.

Boggs teaches protein kinase C antisense oligonucleotides that may contain chimeric RNA/DNA oligos, phosphorothioate oligos, 2'-O-methyl oligos, PNAs and morpholino conjugates. See paragraph bridging columns 6 and 7.

It would have been obvious to one of ordinary skill in the art at the time of the invention to see the invention of Schacht to deliver teach chimeric RNA/DNA oligos, phosphorothioate oligos, 2'-O-methyl oligos, PNAs or morpholino conjugates, because Boggs teaches that such oligos can be used to inhibit protein kinase C function or as in vivo diagnostic reagents (see abstract and column 8, lines 16-34), and because the compositions of Schacht provide improved stability (see page 3, lines 18-24).

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 6/21/04 have been fully considered but they are not persuasive.

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Applicant argues that the polycation of Schacht acts as a "backbone" to which many hydrophilic polymers are attached, whereas the instant invention is essentially the opposite. This argument is unpersuasive because Schacht clearly teaches that the hydrophilic polymers may crosslink the polycations. As such, the hydrophilic polymers can serve as a backbones to which more than one polycation is attached. The instant claims do not exclude this arrangement, and in fact embrace it. Applicant's arguments are unpersuasive because they are based on an arbitrary designation of what constitutes a "backbone". Applicant has presented no evidence or reason why the hydrophilic polymer of Schacht cannot be considered a backbone which cross links polycationic polymers. More importantly, Applicant has failed to point out any specific limitation of the claims that is not taught by Schacht or the supporting references. As such the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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DAVE T. NGUYEN
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Richard Schnizer, Ph.D.